Objectives for Module 1

Knowledge
- Define stroke and transient ischemic attack (TIA), the latter is also called a mini-stroke
- Distinguish ischemic from hemorrhagic stroke
- Describe at least 2 different mechanisms that can produce ischemic stroke

Clinical Applications and Reasoning
- Interpret selected CT scans showing: normal brain, brain with acute hemorrhage, brain with old infarct
- Identify hemorrhagic and ischemic strokes in selected gross specimens
- Explain 1 reason why an individual who has recently had a myocardial infarction might be at increased risk for having a stroke
- Understand the urgency of follow-up testing for a patient who has experienced a TIA

Clinical Applications to Patient Education
- Develop 3 points that you would use in explaining to a patient what a stroke or a TIA is

Overview

A stroke is an injury to the brain caused by interruption of its blood flow, or by bleeding into or around the brain. It produces neurologic deficits that have a relatively sudden onset and persist for more than 24 hours. A stroke can also kill the patient.

Permanent neurologic deficits that are commonly produced by a stroke include:
- Weakness or paralysis
- Loss of sensation
- Problems with vision
- Difficulty in talking or in understanding what is being said
- Difficulty with organization or perception
- Clumsiness or lack of balance
Stroke-related brain injury often evolves over time

A stroke can be triggered by one or a series of sudden vascular events that may last only a few minutes. The resulting damage to some brain cells initiates a series of chemical and cellular events that injure additional brain tissue that was not initially involved. In some strokes, it may be possible to abort these events and “rescue” much or all of the brain. However such a successful rescue requires medical or surgical therapy during the initial minutes and hours after the patient’s signs and symptoms first appear. Knowledge of how best to accomplish this is just now beginning to emerge. The brain continues to respond to its injury over a period that may last a few days or more, but at this later time the goal of therapy is preventing complications and further injury.

A stroke may kill the patient or produce permanent brain damage. If an individual survives a stroke, their specific long-term neurologic deficits will depend on the type and size of stroke, the specific parts of the brain that are involved, the effectiveness of any early medical interventions, treatment and rehabilitation, and characteristics of the individual and his or her family.

### STROKE FACTS – All data refer to the United States (2007 update)

- At least 700,000 people suffer a new or recurrent stroke each year.
- Stroke is the third leading cause of death (150,000 deaths annually).
- From 1994 to 2004 the death rate following a stroke fell 20.4 percent and the actual number of stroke deaths declined 6.7 percent.
- The risk of having a stroke and of dying from one increases with age; yet a significant number of strokes occur in people under the age of 65.
- Over 5 million stroke survivors are alive today –over half being women.
- The annual cost of stroke-related care is estimated at nearly $62.7 billion.
- Strokes can produce serious long-term disabilities. More than half of all stroke survivors are left dependent on others for everyday activities.

**Death soon after a stroke is caused by brain-related or medical complications**

The brain swelling that occurs after a stroke increases intracranial pressure. If there has been hemorrhage, the added volume of blood contributes to the increased pressure. The skull cannot expand. Thus when intracranial pressure increases, “relief” can only be obtained by displacing brain tissue into a different compartment within the skull where the pressure is lower. If the forebrain is swollen, its displacement downward can produce compression of the brainstem. A stroke involving the brainstem itself may also cause swelling and compression. If brainstem injury involves the reticular formation, it may lead to irreversible coma, respiratory arrest, or cardiac failure.
Medical complications following a stroke can include pulmonary embolus due to deep venous thrombosis, pneumonia, or myocardial infarction to name just three. One reason for the recent decrease in mortality after stroke is that prevention of the medical complications of stroke has been steadily improving.

**Aggressive prevention can reduce a patient’s risk of having a first stroke**

Individuals can decrease their risk of stroke and stroke mortality by reducing high blood pressure and hyperlipidemia, cessation of cigarette smoking, moderation of alcohol consumption, increasing physical activity, and careful management of diabetes mellitus and heart disease. Additional medical or surgical treatment can reduce the chances of strokes in individuals who are at particularly high risk, including those who have had a recent TIA (a warning sign of stroke) or myocardial infarction, or those with atrial fibrillation. More remains to be learned about other potentially modifiable risk factors for stroke.

**New therapies administered during an acute ischemic stroke can sometimes reverse or limit brain injury**

In certain cases, new treatments may entirely reverse the course of an acute ischemic stroke or limit the permanent brain injury that it produces. However, their use requires that the patient or family recognize the warning signs of stroke, and reach the hospital within the first 1-2 hours after the stroke has begun.

<table>
<thead>
<tr>
<th>The Five Warning Signs of Stroke</th>
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<tr>
<td>Sudden numbness or weakness of face, arm or leg, especially on one side of the body</td>
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<tr>
<td>Sudden confusion, trouble speaking or understanding</td>
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<tr>
<td>Sudden trouble seeing in one or both eyes</td>
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<tr>
<td>Sudden trouble walking, dizziness, loss of balance or coordination</td>
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<tr>
<td>Sudden, severe headache with no known cause</td>
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(as described in patient education literature of the American Stroke Association)

Ongoing research should provide future physicians with additional ways to limit brain damage once the “triggering” vascular event has occurred. There are also exciting advances in the area of stroke rehabilitation. However at present, physicians are more successful at reducing the chances that a stroke will happen in the first place than of reversing one that has begun or improving post-stroke function.
Strokes can be caused by either blockage or rupture of an artery

Ischemic strokes are produced when an artery is blocked. The resulting inadequate blood flow (ischemia) deprives the brain of oxygen and glucose, and slows the removal of metabolic wastes. The parts of the brain that the occluded artery can no longer adequately supply begin to function abnormally or cease to function. If ischemia persists, brain cells die. The term “infarct” is commonly used to describe such a region of dead tissue. The brain is at special risk for ischemia because there is not enough redundancy in the arterial supply to maintain adequate blood flow if one artery is suddenly occluded. About 88% of all strokes are the ischemic type.

Hemorrhagic strokes are produced by arterial rupture. Depending on what vessels are involved, bleeding can occur within the brain and its ventricles, or around the brain in the subarachnoid space. The blood produces injury by distorting, compressing, and tearing the surrounding brain tissue (including its blood vessels), or by increasing intracranial pressure. About 12% of all strokes are the hemorrhagic type.

Ischemic strokes may be preceded by Transient Ischemic Attacks (TIAs), which are brief Mini-Strokes

A TIA is a brief episode in which neurological deficits suddenly occur, and then disappear completely. Most of these events last only a few minutes to an hour or so, although the strict definition includes events that persist up to 24 hours before they fade. Unlike a stroke, no neurological deficits remain once the attack has ended because little or no brain tissue is permanently damaged. Recent evidence suggests that tissue damage may be more significant than previously believed.

Some strokes occur “out of the blue” but a number of ischemic strokes are preceded by one or more TIAs. Sometimes the symptoms produced by recurrent TIAs are exactly the same each time they occur. Other times the symptoms are different, and can even occur on the other side of the body. Remember that a TIA occurs when an artery is temporarily blocked. If the same region of one artery is being blocked each time, this would produce the same symptoms. How would you explain TIAs that produce different symptoms? (Answer: a different region of the same artery or another artery altogether is being blocked.)

A TIA is an important warning sign of stroke. A TIA is an important warning sign that the stage is set for an ischemic stroke, because it demonstrates that enough vascular and/or cardiac pathology is present to produce neurologic symptoms. Treatments that target the underlying vascular disease can reduce the chances that patients who have experienced TIAs will later have a stroke that produces permanent neurological deficits. We will discuss some of them in later modules.

The term ‘mini-stroke’ is frequently used in discussing TIAs, to emphasize the severity of the event and the importance of obtaining immediate medical attention for an individual who experiences an episode of impaired neurological function, even if it lasts only a few minutes.
If patients don’t tell you about having a TIA, or if you fail to recognize that they are describing a TIA, you will miss an opportunity to intervene and perhaps prevent a stroke!

“Large” arteries and “small” penetrating arteries are both involved in stroke

The vessels that supply the central nervous system originate from the aorta or other great vessels. “Large” arteries are defined as the extracranial portions of the carotid and vertebral arteries and their large intracranial branches, which lie in the subarachnoid space on the surface of the forebrain and brainstem. The large arteries give rise to “small” arteries. These are the vessels that actually enter brain tissue and ultimately branch to form rich capillary beds where oxygen exchange occurs.

The vast majority of ischemic strokes involve narrowing or blockage of large arteries. Hemorrhagic strokes are about equally divided between rupture of large and small arteries.

When ischemic and hemorrhagic strokes do involve the small arteries, the long penetrating branches that supply deep central structures of the forebrain and brainstem (like the thalamus or parts of the basal ganglia or medial pons) are most often implicated. Many people suspect that these slender penetrating arteries are particularly affected by high blood pressure because of their right angle branching and thinner muscular walls. They may also be subjected to higher pressures or more turbulent flow because of their very small diameters. Under sustained high blood pressure, the walls of the penetrating branches can rupture or collapse. The more superficial short branches of small arteries supplying the cortex can also rupture; however this is common only in the very elderly and is not associated with hypertension.

Strokes affect the forebrain most often, the brainstem or cerebellum less often, and the spinal cord rarely. This presumably reflects differences in the volume of tissue, and in the sizes and arrangement of the vessels that supply these regions.

TIA FACTS (2007 Update)

- As many as 15% of patients who have a new stroke retrospectively report one or more prior TIs.
- TIs carry a substantial short-term risk of stroke, hospitalization for cardiovascular events and death.
- Risk of stroke is highest during the 30 days following a TIA. Within a year of a TIA, up to a quarter of patients will die.
More about Ischemic Strokes

About 87% of all strokes are ischemic. They can occur if blood flow is blocked locally in an artery supplying the brain or if the entire circulation fails so that all organs, including the brain, are inadequately perfused (this is what happens in shock).

What might block a brain artery?

1. Atherosclerotic thickening of the wall of the vessel that narrows or even obliterates the lumen (inner channel) through which blood normally flows, or collapse of the wall
2. A “plug” in its lumen formed by material carried in the blood
3. Abnormally high pressure in brain tissue surrounding the vessel that compresses its wall to the point of squeezing shut its lumen

Let’s consider each of these causes of arterial blockage in more detail:

1. Arteries can be occluded by atherosclerotic plaque or other pathology of their walls

Atherosclerosis often develops at the branch points or curving portions of both the extracranial and intracranial large arteries, locations where blood flow is slowed and more turbulent. The internal carotid artery is particularly at risk, although exactly where along its course the disease tends to occur, and how quickly it progresses apparently reflects the individual’s genetic background and additional risk factors that may stimulate plaque growth, such as hypertension and cigarette smoking.

Atherosclerosis involves focal accumulations of lipid, smooth muscle cells, foamy macrophages, and eventually cholesterol crystals, under the surface lining (endothelium) of the artery. With time these accumulations can form elevated plaques that protrude into the vessel’s lumen and significantly reduce blood flow. Perhaps the analogy of a kitchen drain pipe becoming gradually plugged with cooking grease and sludge will help you visualize what is happening.

If occluding the vascular lumen weren’t bad enough, plaques can do a number of additional things that further compromise the brain’s circulation. For instance, a plaque can ulcerate (break open), and the resulting damage to its endothelial lining stimulates the development of thrombus (blood clot), which even further narrows the vessel. What’s more, pieces of thrombus or fragments of an exposed plaque core can be swept along by the blood flowing through the vessel, becoming emboli (discussed next)

Atherosclerotic plaque can form in the walls of small as well as large arteries. However, there are several additional kinds of pathology that particularly affect the walls of small arteries, leading to their collapse and blockage of blood flow.

2. Arteries can be plugged by thrombus or embolus in the lumen

A thrombus is a solid mass of platelets and/or fibrin (and other components of blood) that is formed locally in a vessel. Thrombi form when the clotting mechanism gets turned on. This is supposed to happen when you are injured. However it can also occur at the site of an ulcerated
atherosclerotic plaque, or whenever the endothelial cells that line the inner surface of an artery have been damaged. Thrombus formation may also occur in places where blood flow is sluggish, enabling clotting factors to activate and giving platelets more opportunity to stick together. Disorders of blood cells (for instance sickle cell disease) or blood proteins can increase the chance of thrombus formation, and therefore contribute to the risk of ischemic stroke.

An embolus is most often a piece of a thrombus that has broken free and is carried toward the brain by the bloodstream. The term thromboembolus is used a lot because it turns out that most emboli arise from thrombi, although bits of plaque, fat, air bubbles, and other material also qualify as emboli. Presumably an embolus floats along with the flowing blood until it encounters a narrowing in the artery through which it cannot pass. When the embolus gets stuck, it blocks the artery, reducing blood flow to downstream tissues, thus rendering them ischemic.

### Three Important Sources of Emboli to the Brain

- **Thrombus that initially formed within the diseased heart.** For example, the irregular, ineffective contractions of the heart muscle seen in atrial fibrillation lead to blood pooling in the left atrium and increased thrombus formation. Thrombus can also form in the left ventricle if the pumping action of the heart is suboptimal because of a myocardial infarction. Bits of these thrombi enter the systemic circulation as emboli that can travel to any organ, including the brain.

- **Thrombus that forms on a heart valve.** A thrombus that forms on a heart valve is called a vegetation because it is shaped like a small shrub. Vegetations are more common in the left heart because the higher pressures that slam shut the mitral and aortic valves cause them to be injured more frequently. Bacteria can grow in thrombi. Pieces of both infected and noninfected vegetations can break off and form emboli.

- **Thrombus associated with atherosclerotic plaque that formed in the extra- or intracranial parts of a carotid or vertebral artery.** A bit of the thrombus breaks off and is carried more distally in the same vessel by the flowing blood (this is called artery-to-artery embolism).

Regardless of its source, an embolus does its damage by getting stuck in a large artery or branch and blocking blood flow beyond that point.

The diameters and branching patterns of the large arteries seem to have a lot to do with where embolic material tends to travel, and where it tends to ultimately lodge. For instance, the large diameter, gently curving course, and rapid blood flow in the middle cerebral artery put it at particular risk for embolism – and therefore the regions of brain that it supplies at risk for embolic stroke. The smaller anterior cerebral artery, which originates from the internal carotid at a sharper angle, captures emboli less often – emboli apparently don’t corner well!

### 3. Local pressure in brain tissue can shut down circulation in its small arteries.

Blood or other fluid in the extracellular space, or swollen brain cells themselves can increase local pressure to the point of shutting down blood flow in smaller arteries.
The size and location of an ischemic infarct is related to the brain region that the occluded portions of an artery supplied prior to the stroke.

So far, we have been talking primarily about the results of blocking large arteries. However, occlusion of the class of small arteries that supply deep forebrain or medial brainstem structures can cause small or “lacunar” strokes. Lacunar strokes have earned their name because the area that is infarcted takes the form of a small lacune or cavity (usually less than 15mm in diameter).

Although a lacunar infarct may be small, it can lead to major neurologic deficits. A much larger infarct may actually produce a less extensive (or intrusive) neurologic deficit for the patient. It all depends on exactly what gray and white matter structures are involved.

During a Transient Ischemic Attack an artery is temporarily blocked.

One mechanism explaining what happens during a TIA is embolization of thrombus formed on plaques in the extracranial portions of the carotid and vertebral arteries or in the diseased heart. This material travels into a brain artery and briefly plugs it up, reducing blood flow to a particular region and cauging it to malfunction. However if the thrombus quickly breaks up and circulation through that part of the vessel is re-established, and function returns. Since little if any brain tissue has actually died, the patient has no permanent neurologic deficit. A second mechanism to explain TIAs is a low perfusion state, usually resulting from carotid artery stenosis.

There is really no such thing as a transient hemorrhagic attack. The reason that it would be very unusual for hemorrhage into brain tissue to cause transient, focal neurological deficits is that the signs/symptoms can be reversed only when the blood has been removed -- a process that takes weeks or months, not minutes.

A TIA is a warning of impending ischemic stroke. Tests are now available to help identify the vascular pathology responsible for a patient’s TIA. This information is key in identifying the most appropriate medical or surgical treatment – treatment which has been shown to help prevent stroke and save lives.

Some Clinical Thoughts about TIAs

Repeated brief TIAs producing the same neurological deficits are often the warning signs that a particular major vessel contains dangerously unstable atherosclerotic plaque on which thrombi are repeatedly forming and then fragmenting. The neurological features of these TIAs often reflect the deficit, or part of the deficit, that would be produced by the impending “completed” stroke. It is less likely that cardiac emboli will repeatedly produce the same deficients – they are able to travel to any part of the brain. In some individuals, TIAs may result from decreased perfusion of large arteries that are already partially occluded by plaque. This might occur with fluctuations in blood pressure produced by medication or by various cardiac arrhythmias.
More about Hemorrhagic Strokes

About 13% of all strokes are hemorrhagic. One major cause is rupture of either **aneurysms** (abnormal outpouchings of large arteries) which initially bleed into the subarachnoid space, or of **arteriovenous malformations** (abnormal vessels) which are often located within the brain and therefore tend to bleed into the brain itself. Both of these pathologies are thought to be the consequence of developmental abnormality, and are characterized by thinned vascular walls.

Aneurysms commonly form at the branch points of large intracranial arteries. Aneurysms often announce their presence only when they rupture. Less often they reveal themselves by compressing neighboring structures and producing neurologic symptoms. In addition, aneurysms or sometimes arteriovenous malformations may bleed a little, producing sudden unexplained headache, seizure, or other neurological disturbance prior to a more massive rupture. Such warnings may make it possible to identify the problem, and to initiate surgical or endovascular intervention if it is indicated.

The other major cause of hemorrhage is rupture of the walls of the small penetrating arteries serving deep structures, with bleeding directly into the brain and its ventricles (**intracerebral hemorrhage**). As discussed previously, these vessels are at particular risk because of their thin muscular walls and small lumens. It is thought that the cumulative effects of untreated hypertension and atherosclerosis or other kinds of pathologic changes weakening their walls, puts them at special risk for rupture.

The neurologic deficits produced by hemorrhagic strokes can reflect damage to regions of the brain remote from the leaking artery. There are several reasons for this: (1) when an artery is ruptured, blood under arterial pressure is forcefully shot into the brain. (2) Increased intracranial pressure due to the sudden addition of hemorrhaging blood can compress and distort brain tissue located at some distance from the site of arterial rupture.

Finally, we should point out that not all strokes fall neatly into the categories that we have described. There remain strokes whose causes baffle even the experts. Other causes of strokes are beyond the scope of this introduction. One of these is amyloid angiopathy, a pathology of small vessels in the very elderly which has a role in **lobar hemorrhages**.

**Advanced Information about Lobar Hemorrhages**

It has recently been recognized that small arteries supplying the superficial regions of the cerebral hemispheres may develop deposits of an abnormal protein called amyloid in the extremely elderly. In some cases, this material can weaken the walls of these vessels to the extent that they rupture and cause hemorrhages in the superficial regions of the hemispheres. These are referred to as lobar hemorrhages (presumably because they involve outer portions of the various lobes of the brain).

Unlike the intracerebral hemorrhages involving midline penetrating vessels, superficial lobar hemorrhages often occur in individuals who have had normal blood pressure throughout their lives.
# Introduction to CT Scans

## What CT scans can show about ischemic and hemorrhagic stroke

A CT (Computed Tomography) scan is usually the first radiologic test used when a patient presents with neurologic symptoms suggesting a stroke or TIA. It is used to exclude the presence of hemorrhage, which is an essential step if the administration of “clot-busting” drugs is being considered.

A CT scan produces a picture of a slice of the brain, in which its features are made visible by how much they attenuate (in other words, absorb or deflect) x-rays that have been passed through them. Detectors positioned around the circumference of the scanner collect readings from multiple angles. This numerical information is fed into a computer, which reconstructs a gray-scale visual image of the brain slice. These images of the brain are optimized to show the subtle tissue difference between gray and white matter. (The major reason for this difference is the large amount of “fatty,” lipid-rich myelin surrounding axons in the white matter in comparison to the gray matter, which contains many myelinated axons but also numbers of neuron cell bodies and dendrites that are not myelinated.)

<table>
<thead>
<tr>
<th>Simplified Display of CT Brain Tissue Image Characteristics</th>
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<tbody>
<tr>
<td><strong>Bright (This means high attenuation of x-rays)</strong></td>
</tr>
<tr>
<td>Calcified tissues (bone, calcified areas of choroid plexus* and pineal gland**)</td>
</tr>
<tr>
<td>Brain tissue and its blood vessels</td>
</tr>
<tr>
<td>Fat</td>
</tr>
<tr>
<td>Water and CSF</td>
</tr>
<tr>
<td>Air</td>
</tr>
<tr>
<td><strong>Dark (This means low attenuation of x-rays)</strong></td>
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*Recall that the choroid plexi are specialized tissues that produce the CSF, and are found in specific parts of the ventricular system. In most adults certain regions of the choroid plexi become calcified.

** The pineal gland is a single unpaired structure that lies in the midline of the brain. It is located just rostral to the superior colliculus and has the shape of a little pine cone that is oriented with its tip pointing toward the occipital lobes (posterior). It also becomes partially calcified by the teenage years.

By convention, images are always shown as though you were standing below the patient’s head and looking up at the brain – this means that the patient’s left is on the right side of the image.

Practical Hint: The brain is largely a symmetrical structure – when you are trying to find areas of damage, try looking for regions in which the left side and the right side appear different.
When there is acute hemorrhage into the brain or a large thrombus with its entrapped red blood cells in a vessel, the accumulated hemoglobin makes the area or vessel look bright. After the hemoglobin is removed by phagocytes, the bright area disappears.

If brain tissue has actually been killed and the destroyed remnants removed (this occurs months after the injury), what would you predict about the appearance of the affected area on CT? Answer: it would be more like water-CSF, so it would look dark.

When there is ischemia in the brain, the water content of the affected brain tissue increases and it swells. How do you think this would change the appearance of the affected brain tissue as seen on CT scan? Answer: the increased water content would make it look somewhat darker. These changes cannot be visualized immediately! Depending on just which area of the brain is involved, they begin to be seen on CT scans after about 12-18 hours. This means that very early ischemic strokes are not detected on routine CT scans. (CT scans in the first hours of symptom onset are used to exclude hemorrhagic stroke, rather than confirm ischemic stroke.) As ischemic damage continues to evolve, however, the additional changes make these areas visible on CT scans.

Simplified Display of CT Brain Tissue Image Characteristics - STROKE

Bright (This means high attenuation of x-rays)
- Calcified tissues (bone, calcified areas of choroid plexus and pineal gland)
  CLOTTED BLOOD
- Brain tissue and its blood vessels
  BRAIN TISSUE SWOLLEN SECONDARY TO ISCHEMIC INJURY
- Fat
- Water and CSF AREA WHERE BRAIN TISSUE HAS DIED AND BEEN REMOVED
- Air

Dark (This means low attenuation of x-rays)